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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/633,630 | 08/05/2003 | Klaus Giese | 39078-0005 | 6369 |

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/633,630 | GIESE ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly Chong | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27,29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,29, 31 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of Group I, claims 1-27, 29 and 31-32 in the reply filed on 04/14/2005 is acknowledged.

Claims 28 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/14/2005.

### *Status of the Application*

Claims 1-27, 29 and 31-32 are pending and currently under examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27, 29 and 31-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 are drawn to "a ribonucleic acid comprising a double stranded structure". A ribonucleic acid is simply A, C, G or U and therefore cannot comprise a double stranded structure. Claims 2-27, 29 and 31-32 are rejected as being dependent upon claims 1 and 11.

Claims 11 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "wherein the pattern of modified..." in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "wherein the pattern of modified..." in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "wherein the pattern of modified..." in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7, 9-10, 19, 24, 29 and 31-32 rejected under 35 U.S.C. 102(b) as being anticipated by Kool (US Patent No. 5,514,546).

Claim 1 is drawn to a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially complementary to

target molecule and wherein the double stranded structure is blunt ended on one or both ends. Claims 2-5 further limit claim 1 by stating the first and/or second stretch have a length of 18 or 19 nucleotides in length, blunt ended on both ends and optionally comprises a second stretch of nucleotides that are not complementary to the target nucleic acid. Claims 6 –7 and 9-10 recite the limitations wherein the double stranded structure has at least one strand with an overhang of at least one nucleotide at the 5' end or 3'-end, the overhang consists of at least one nucleotide selected from a ribonucleotide or deoxyribonucleotide and one nucleotide has a modification selected from a fluoro, methoxy, alkoxy and alkyl. Claim 19 limits claim 1 by stating the first strand and the target strand are perfectly complementary to each other. Claim 24 further limits claim 1 by reciting the first and second strand are linked by a loop structure. Claims 29 and 31-32 limit claim 1 by stating the ribonucleic acid is in a pharmaceutical composition and an organism comprising a cell.

Kool discloses a double stranded structure wherein the first stretch is partially complementary to a target molecule and wherein the double stranded structure is blunt ended on both ends (see Figure 1). Kool further discloses the double stranded structure can have strands from 4 to 100 nucleotides, preferably 6-20 nucleotides in length (see column 7, lines 5-9). Kool additionally discloses a stand can have an overhang (see column 6, lines 56-61), the overhang can consist of ribonucleotides and deoxyribonucleotides (see column 13, lines 10-37) and further the modification can consist of an alkoxy or alkyl (see column 13, lines 44-47). Kool discloses double stranded structures wherein the first and second strands are linked by a loop structure (see column 17, lines 50-55) and further teach the first strand and the target nucleic acid can be perfectly complementary to each other (column 8, lines 16-22). Kool additionally discloses a

cell and organism comprising a ribonucleotide (see column 14, lines 28-68) and further discloses a pharmaceutical composition comprising the ribonucleotide and a pharmaceutically acceptable carrier (see column 28, lines 56-60).

Thus, Kool anticipates claims 1-7, 9-10, 19, 24, 29 and 31-32 of the instant application.

Claims 1-7, 9-12, 16-19, 29 and 31-32 rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (US 2004/0229266).

Claim 1 is drawn to a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially complementary to target molecule and wherein the double stranded structure is blunt ended on one or both ends. Claims 2-6 further limit claim 1 by stating the first and/or second stretch have a length of 18 or 19 nucleotides in length, blunt ended on both ends and optionally comprises a second stretch of nucleotides that are not complementary to the target nucleic acid and further wherein at lease one strand has an overhang of at least one nucleotide at the 3' or 5' end. Claims 7 and 10 recite the limitations wherein the overhang consists of at least one nucleotide selected from a ribonucleotide or deoxyribonucleotide and the nucleotide modification is at the 2' position. Claims 11-12 and 16-18 are drawn to a double-stranded structure wherein the first or second strand comprises a plurality of groups of modified nucleotides modified at 2' position, flanked by modified or unmodified nucleotides that consist of one to ten nucleotides, the modification at the 2' position is selected from the group as listed in claim 16, the double stranded structure is blunt ended at one or both ends. Claim 19 limits claim 1 by stating the first strand and the target strand are perfectly complementary to each other. Claim 24 further limits claim 1 by reciting the

first and second strand are linked by a loop structure wherein the loop structure comprises a non-nucleotide acid polymer or is comprised of a nucleic acid. Claims 29 and 31-32 limit claim 1 by stating the ribonucleic acid is in a pharmaceutical composition and an organism comprising a cell.

Tuschl et al. discloses a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially or perfectly complementary to target molecule (see paragraph 0017) and wherein the double stranded structure is between 19-25 nucleotides, is blunt ended on one or both ends or has at least one strand with an overhang (see paragraphs 0009 and 0136 and Figure 11). Tuschl et al. further discloses the double stranded structure comprises a plurality of groups of modified nucleotides modified at 2' position, flanked by modified or unmodified nucleotides that consist of one to ten nucleotides, the modification at the 2' position can comprise a methoxy (see paragraph 0016 and Figure 14). Tuschl et al. further disclose a ribonucleic acid in a pharmaceutical composition (see paragraph 0031) and a cell in an organism comprising the ribonucleic acid (see paragraph 0028).

Thus, Tuschl et al. anticipates claims 1-7, 9-12, 16-19, 29 and 31-32 of the instant application.

Claims 1-3, 7-12, 16-17, 19, 21-25, 27, 29 and 31-32 rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen et al. (US 2003/0190635).

Claim 1 is drawn to a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially complementary to target molecule and wherein the double stranded structure is blunt ended on one or both ends.

Claims 2-3 further limit claim 1 by stating the first and/or second stretch has a length of 18 or 19 nucleotides in length. Claims 7-10 recite the limitations wherein the overhang consists of at least one nucleotide selected from a ribonucleotide or deoxyribonucleotide, the overhang consists of a modification consisting of inverted abasic nucleotides and the nucleotide modification is at the 2' position. Claims 11-12, 16-17 and 21-23 are drawn to a ribonucleic acid comprising a double-stranded structure wherein the first or second strand comprises a plurality of groups of modified nucleotides modified at 2' position, flanked by modified or unmodified nucleotides that consist of one to ten nucleotides, the modification at the 2' position is selected from the group as listed in claim 16, the double stranded structure is blunt ended at one or both ends. Claim 19 limits claim 1 by stating the first strand and the target strand are perfectly complementary to each other. Claims 24-25 and 27 recite the first and second strand are linked by a loop structure. Claims 29 and 31-32 limit claim 1 by stating the ribonucleic acid is in a pharmaceutical composition and an organism comprising a cell.

McSwiggen et al. discloses a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially or perfectly complementary to target molecule (see paragraph 0017 and 0121) and wherein the double stranded structure is between 19-25 nucleotides (see paragraph 0035). McSwiggen et al. further discloses the double stranded structure comprises a plurality of groups of modified nucleotides modified at 2' position, flanked by modified or unmodified nucleotides that consist of one to ten nucleotides, the modification at the 2' position can comprise a methoxy or flouro, the overhang can be an inverted abasic and wherein the modified nucleotide on the first strand is aligned with an unmodified nucleotide on the second strand (see Figure 5). McSwiggen et al. further disclose

the ribonucleic acid first and second strand are linked by a loop structure (see paragraph 0061 and Figure 6). McSwiggen et al. further disclose a ribonucleic acid in a pharmaceutical composition (see paragraph 00198) and a cell in an organism comprising the ribonucleic acid (see paragraph 0027).

Thus, McSwiggen et al. anticipates claims 1-3, 7-12, 16-17, 19, 21-25, 27, 29 and 31-32 of the instant application.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 19-20, 24, 29 and 31-32 are rejected as being unpatentable over Kool (US Patent No. 5,514,546) in view of Beigelman et al. (US Patent No. 6,617,438) and further in view of Holen et al. (Nucleic Acids Research, 2002: Vol. 30, No. 8).

Claims 8, 10 and 20 of the instant application are drawn to a double stranded structure wherein the overhang comprises at least one nucleotide having a modification selected from the group consisting of inverted abasic nucleotides, having nucleotides having NH2-modifcations at the 2'-position, wherein at least one nucleotide having a modification at the 2'-position selected from the group consisting of fluoro, methoxy, alkoxy and alkyl and further wherein the first strand and the target nucleotide has one mismatch or two mismatches.

The teachings of Kool are relied upon for the reasons outlined in the above 102 rejection. Kool does not teach the overhang comprises inverted abasic nucleotides or nucleotides having NH2-modifcations at the 2'-position, wherein at least one nucleotide having a modification at the 2'-position selected from the group consisting of fluoro, methoxy, alkoxy and alkyl or teach the first strand and the target nucleotide has one or two mismatches.

Beigleman et al. teach inverted abasic nucleotide modifications to the terminus of the oligonucleotide and further teach the nucleotide can comprise an NH2 or fluoro at the 2'-position.

Holen et al. teach dsRNAs containing either one or two mismatches relative to an mRNA (see page 1763, column 1, second paragraph and Figure 6). Holen et al. teach that incorporating mismatches in dsRNAs are desirable to investigate the tolerance of the RNAi system for mismatches in the siRNA relative to the mRNA target. Figure 6 exemplifies the tolerance of RNAi for one or two mutations of the dsRNAs relative to the target mRNA.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the modifications, as taught by Beigleman et al. and the mutations of dsRNA relative to a target gene, as taught by Holen et al. into the dsRNA molecule taught by Kool et al.

One would have been motivated to make a dsRNA with inverted abasic nucleotide modifications to the terminus of the oligonucleotide and modifications at the 2'-position because Beigleman et al. specifically teach such modifications protect the nucleic acid molecule from exogenous degradation and help in delivery and localization in the cell (see column 9, lines 16-68). Further, one would have been motivated to incorporate single one or two mutations in the

dsRNAs because Holen et al. expressly teach dsRNA with one or two mismatches relative to the target gene and such mutations would be desirable to investigate the tolerance of the RNAi system for mismatches and would additionally facilitate the design of dsRNA for specific targeting of mRNA that contain nucleotide polymorphisms.

Finally, one would have a reasonable expectation of success because Beigelman et al. teach inhibition of an mRNA using oligonucleotides with inverted abasic nucleotide modifications to the terminus of the oligonucleotide and modifications at the 2'-position and Holen et al. teach making dsRNAs with one or two mismatches relative to an mRNA, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3, 7-8, 10-14, 16-17, 19, 21-25-27, 29 and 31-32 rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (US 2003/0190635) in view of Crooke et al. (US Patent No. 5,898,031) and in further view of Kool (US Patent No. 5,514,546).

Claims 13-14 of the instant application are drawn to a double stranded structure comprising a pattern of modified nucleotides. Claim 26 of the instant application is drawn to a ribonucleic acid comprising a double-stranded structure wherein the structure further comprises a non-nucleic acid polymer loop.

The teachings of McSwiggen et al. are relied upon for the reasons outlined in the above 102 rejection. McSwiggen et al. does not teach a double stranded structure with a pattern of

modified nucleotides and further does not teach the loop structure comprises a non-nucleic acid polymer.

Crooke et al. disclose a ribonucleic acid compound with modified nucleotides which are flanked by unmodified nucleotides and further teach oligoribunucleotides can be assembled from plurality of such subunits, therefore forming a pattern of modified and unmodified nucleotides (see Figure 1 and columns 9, 11 and 13, lines 35-44, 15-18 and 21-45, respectively).

Kool et al. disclose a ribonucleic acid double stranded structure comprising a non-nucleic acid loop structure (see paragraph 17, lines 50-65).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the pattern of modified and unmodified ribonucleotides, as taught by Crooke et al. into the double stranded structure as taught by McSwiggen et al. Further it would have been obvious to incorporate the non-nucleic acid polymer, as taught by Kool et al. into the loop structure of the double-stranded ribonucleic acid taught by McSwiggen et al.

One would have been motivated to make a double stranded structure with modified and unmodified ribonucleic acids in such a pattern because such a pattern increases the affinity of the oligoribonucleic acid compound to the target (see Crooke et al., column 9, lines 25-44). One would have been motivated to make a non-nucleic acid polymer loop structure because non-nucleic acid loop domains are less expensive to produce, are more resistant to nucleases, have a greater binding affinity and can better penetrate cellular membranes (see Kool et al., column 17, lines 55-64).

Finally, one would have a reasonable expectation of success because Kool et al. teach strong target binding and greater stability by stem-loop oligonucleotides (see Examples 1 and 2).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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